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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 09/778,259 | 02/07/2001 | Cristobal Guillermo dos Remedios | 13388 | 4496 |

7590 10/26/2006

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| EXAMINER |
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CHEU, CHANGHWA J

| ART UNIT | PAPER NUMBER |
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1641

DATE MAILED: 10/26/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/778,259

Applicant(s)

REMEDIOS ET AL.

Examiner

Jacob Cheu

Art Unit

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 15 August 2006.
2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 38 and 42-45 is/are pending in the application.
4a) Of the above claim(s) _____ is/are withdrawn from consideration.
5) ☐ Claim(s) _____ is/are allowed.
6) ☒ Claim(s) 38, 42-45 is/are rejected.
7) ☐ Claim(s) _____ is/are objected to.
8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- 1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08)
Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicant's amendment filed on 8/15/2006 has been received and entered into record and considered.

The following information provided in the amendment affects the instant application:

1. Claims 1-37 and 39-41 are cancelled.
2. Claims 38, 42-45 are under examination.

Claim Rejections - 35 USC § 103

1. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

2. The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

3. The rejections of claim 38, 42-43 are rejected under 35 U.S.C. 103(a) as being unpatentable over Liu et al. (J. Inorganic Biochemistry 1998 Vol. 71, page 1-6) in view of Pisanti et al. (Marine Pollution Bull (1988) Vol. 19, page 328-333) are maintained.

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Liu et al. teach a method of measuring fluorescence quenching of DNA bound fluorescence dye, e.g. increase dissociation or inhibition of fluorescent dye bound to the DNA, by a sample containing a metal atom, i.e. copper (II) (See abstract). Liu et al. teach that the presence of copper (II) metal would compete with binding the DNA molecule intercalated with the fluorescence ethidium dye (See abstract; Results and Discussion). The binding constant of the copper is around 10^{-10} (M^{-1}) which falls within the range of micromolar (See Figure 1). However, Liu et al. do not explicitly teach detecting the inhibition or dissociation of the dye on the DNA as an indication of the presence of a metal.

Pisanti et al. teach the presence of metals in the ecosystem, e.g. ocean or rivers, is of great concern because of the potential to impact the quality and physiology of marine organisms (page 328, left column, first paragraph; page 330, right column, last paragraph). Pisanti et al. teach metal levels, such as copper, are essential for the biological equilibrium of the marine ecosystem. Supra.

Therefore, it would have been obvious to one ordinary skill in the art at the time the invention was made to have motivated Liu et al. to measure the presence of copper in an aquatic sample as taught by Pisanti et al. because Liu et al. has developed an effective fluorescence quenching assay for the heavy metal, and monitoring metals in the environmental is of great concern for maintaining quality of ecosystem.

With respect to claim 43, Liu et al. use ethidium bromide as the fluorescence dye (See page 2, Section 2.1 Materials and Methods).

4. The rejections of claim 44-45 are rejected under 35 U.S.C. 103(a) as being unpatentable over Liu et al. in view of Pisanti et al. and further in view of Gold et al. (US 624246) are maintained.

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Both Liu et al. and Pisanti et al. references have been discussed but are silent in teaching use of a solid support for immobilization of DNA for analysis.

Gold et al. teach an efficient and sensitive screening for DNA binding agents by immobilizing DNA on solid support and measuring the change of dye, e.g. fluorescence, for indicative of the presence of the binding agent (Col. 13, line 25-345; Figure 4-5).

Gold et al. teach a variety of choices for solid support, including glass, polystyrene, gold or silicon (Col. 6, line 42-50).

Therefore, it would have been obvious to one ordinary skill in the art at the time the invention was made to have provided both Liu and Pisanti et al. with the solid support for immobilization of DNA for better efficiency since it is well-known for immobilization of molecule on a solid support to increase sensitivity of the assay and the methodology employed by Gold et al. in also in an analogous field, e.g. measuring change of fluorescence dye for indicative of DNA binding agents.

Response to Applicant's Arguments

Applicant argues that Liu et al. reference distinguishes from the instant invention because Liu et al. reference is performed in a "controlled conditions" (emphasis by applicant; See Remarks page 2, last paragraph). Under such condition, it avoids a variety of wide variation, including salt concentration, pH, and other factors related to the environmental samples.

Applicant arguments have been considered, but are not persuasive.

The crux of the Liu et al. reference demonstrates that heavy metal, such as copper, is capable of replacing fluorophore (e.g. quenching) resulting in a decrease of the ethidium bromide intercalating with the DNA base pair and the binding constant of the nucleic DNA molecule to the fluorescent bromide dye (See Abstract). It is this main concept coupling with the

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concern/needs for environmental heavy metal pollution (See secondary reference by Pisanti et al.) to render the instant invention obvious. When one ordinary skill in the art testing each individual sample, the sample alone also has a “controlled condition”, namely fixed salt, pH and other factors. Furthermore, the case law has established that it would have been obvious to one ordinary skill in the art at the time the invention was made to adjust the working condition, since it has been held that the provision of adjustability, where needed, involves only routine skill in the art. In re Stevens, 101 USPQ 284 (CCPA 1954). In addition, standardizing samples prior to analysis, e.g. fixed pH or buffer salts treatment, is widely practiced and routinely optimized in the laboratory. Thus the factors of pH or salts or other factors would have been minimized to one ordinary skill in the art.

Applicant argues that it is improper to combine both Liu and Pisanti et al. references since no motivation or suggestion nor any reasonable expectation success could be produced. Applicant argues that Liu et al. disclose copper (II) macrocyclic complexes but not other metal complexes, or metal ions in general, can also intercalate into the DNA to cause replacement of the DNA-bound fluorescent dye. Furthermore, Pisanti et al. disclose the effect of various heavy metal or transitional ions or radicals (including copper) on microorganisms. In addition, Pisanti et al. tested the microorganisms in a cultural medium containing chloride salts. Thus, taken together, one ordinary skill in the art would appreciate that there is no reasonable expectation of success in combining both references.

Applicant arguments have been considered, but are not persuasive.

As indicated in the previous and the present Office Action, Pisanti et al. provided the motivation and suggestion to one ordinary skill in the art to combine the teachings of Liu et al in measuring the environmental heavy metal contamination, e.g. copper. Second, the claim language is an open language “a toxicant comprising a metal atom”. The copper can exist in different forms in the environment. The claim does not limit or restrain any particular form of toxicant as long as the toxicant contains a “*metal atom*” (emphasis added). With respect to the

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possible interference of chloride salts, examiner had discussed before and this relates to the optimization or adjustability of the assay, and would be obvious to one ordinary skill in the art.

Applicant argues that Liu et al. reference in fact teaches away from using fluorescent quenching assays for study other metal complex.

Applicant arguments have been considered, but are not persuasive.

As recited in the claim, applicant does not specify any form or particular heavy metal, Liu et al. reference at least showed copper can replace fluorescent dye from DNA and decrease the binding constant. Copper is a metal and Liu et al. reference encompasses the instant invention.

Applicant argues that the Gold et al. reference is not a proper art to be combined with the Liu and Pisanti et al. Applicant reasons that the disclosure of Gold relates to the detection of a molecule that base pair with immobilized DNA, whereas the instant invention does not disrupt the base pair but rather changes the structure to sufficiently perturb the release of the fluorescent dye.

Applicant arguments have been considered, but are not persuasive.

The motivation and suggestion to use Gold et al. reference is to immobilize DNA on a solid support for better efficiency and it is well-known and widely practiced in the art. With respect to whether the binding would disrupt the base pairing, it is not pertinent because the ultimate aim is for measuring the change of fluorescent dye from the intercalated DNA molecules, whether structures remain intact or disrupted.

Conclusion

5. No claim is allowed.

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6. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire **THREE MONTHS** from the mailing date of this action. In the event a first reply is filed within **TWO MONTHS** of the mailing date of this final action and the advisory action is not mailed until after the end of the **THREE-MONTH** shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than **SIX MONTHS** from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jacob Cheu whose telephone number is 571-272-0814. The examiner can normally be reached on 9:00-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Long Le can be reached on 571-272-0823. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

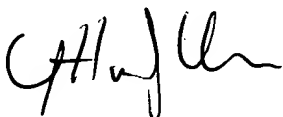
Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Jacob Cheu

Examiner

Art Unit 1641

October 18, 2006



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